FINAL REPORT

PROTOCOL CP 411 EXPLANT TESTING: DETERMINATION OF MOISTURE, PROTEIN, AND FAT

DATA REQUIREMNET

21 CFR PART 58 GOOD LABORATORY PRACTICES STANDARDS

AUTHOR

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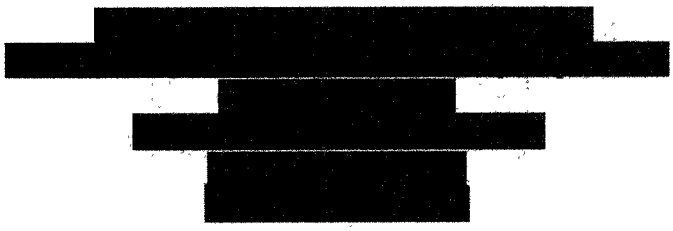
STUDY INITIATION DATE
April 01, 2004

STUDY TERMINATION DATE
August 31, 2004

TEST FACILITY



PROJECT NUMBER
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SPONSOR

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2005-4101BL_01_04_CP411-MENTOR

STATEMENT OF CONFIDENTIALITY CLAIMS

Information claimed confidential on the basis of its business, products, laboratory analysis, and evaluation of mammary implants. The information is considered proprietary, confidential, and valuable to Mentor Corporation.

Grace Chiang 08/10/04
(DATE)
Mentor Corporation

GLP COMPLIANCES STATEMENT

I certify, as a study director, that this study was conducted in accordance with 21 CFR Part 58 FDA Good Laboratory Practices Standards.

CKT 08/09/04

Chee Kai Tan, Ph.D. (DATE)
Study Director
[redacted]

APPROVED:

R. Karimi

Reza Karimi, Ph.D. (DATE)
Director
[redacted]

08/10/04

Grace Chiang Dept (DATE)
Principal Scientist
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Quality Assurance Unit Statement of Compliance

It is the intent of Southwest Research Institute that all studies conducted by our facility shall be of the highest quality and meets or exceeds the criteria promulgated by the FDA CFR 21 part 58 to assure the quality and integrity of the data generated. Study protocol CP 411 (SwRI Study 01.12058.02.00X). Explant Testing: Determination of Moisture, Protein, and Fat, was inspected by the [redacted] Quality Assurance Unit and the findings submitted to the Study Director and Management on the following dates:

Inspection Type	Inspection Date	Submitted to Study Director& Management
Protocol Review/Training files	04-05-04	04-05-04
Sample/Std. Prep Analysis (Amino Acids)	04/26/04	04/26/04
Sample/Std. Prep Analysis (Moisture)	04-27-04	04/27/04
Sample/Std. Prep Analysis (Fat)	05/21/04	05/21/04
Data Review	08/09/04	08/09/04
Final Report Review	08/09/04	08/09/04

The [redacted] Quality Assurance Unit audited the raw data, all records, and the report. Documentation and verification of these inspections have been archived. The report was found to be an accurate reflection of the study and the data generated. All raw data will be maintained in the quality system archives.

Jo Ann Boyd 8/9/04

Jo Ann Boyd, Manager (Date)
Quality Assurance Unit
[redacted]

TABLE OF CONTENTS

1. INTRODUCTION

The objective of this study was to determine moisture, protein, and fat in explanted intact Mentor Gel-Filled Mammary Implants. The ASTM method E203-01 (E15.01), Standard Test Method for Water Using Volumetric Karl Fisher Titration, will be used to determine the moisture content (SwRI TAP 01-0406-131). [redacted] standard operating procedures (TAP 01-0408-078 HPLC Determination of Amino Acids Using The Waters ACCQ-TAG Method) will be used for the acid hydrolysis of protein and followed with amino acids assay. A FT-IR (TAP 01-0203-035 Quantitative Determination of Fat in Explant Materials by FTIR) method will be used for fat determination. The study was conducted in accordance with the Mentor's study protocol (Attachment A – Protocol CP 411, Explant Testing: Determination of Moisture, Protein, and Fat) guidelines. All methods including the sample preparation and the instrumental procedures will be validated to ensure the reliability and accuracy.

2. TEST AND REFERENCE SUBSTANCES

2.1 Test Substances – Explants and autoclaved unimplanted controls of gel-filled mammary implants

Table 1. Sample List – Sample Description and Traceability

Sample No.	Description	Size	Catalog No.	File No.	Date of Implantation	Days in Vivo	Lot No.
1	Smooth Round Moderate Profile Gel-Filled Mammary Implant (Expant)	450cc	350-7450BC	971875	11/11/1993	1,290	47073
2	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Explant)	250cc	354-2507	200101-0558	Mid 1994	2,330	50938
3	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Explant)	350cc	354-3507	200302-0663	Early 1994	3,249	57883
4	Smooth Round Moderate Profile Gel-Filled Mammary (Unimplanted Control)	250cc	350-7250BC	NA	NA	NA	57529

Sample No.	Description	Size	Catalog No.	File No.	Date of Implantation	Days in Vivo	Lot No.
5	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Unimplanted Control)	100cc	354-1007	NA	NA	NA	60228
6	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Unimplanted, unautoclaved)	100cc	354-1007	NA	NA	NA	60228
7	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Unimplanted, unautoclaved), for exploratory work and method applicability	100cc	354-1007	NA	NA	NA	60228

2.2 Reference Substances

2.2.1 List of Reference Standards for Moisture Analysis

Methyl Alcohol, Anhydrous
CAS # 67-56-1
Supply: Acros Research Products
Purity: 99.8 %
Storage Condition: Below -4 °C
Cat. #: 41377-5000
Lot No.: B0507242
Expiration Date: November 2005

Water Standard, Aqualine
CAS #: 7732-18-5
Supply: Fisher Scientific Company
Purity: 5 mg/mL

Storage Condition: Below -4 °C
Cat. No.: AL2730
Lot #: 025848
Expiration Date: March 2005

2.2.2 List of Reference Standards for Fat Analysis

Corn Oil
CAS #: 8001-30-7
Supply: Spectrum Laboratory Product
Purity: 99.0 %
Storage Condition: Below -4 °C
Cat. No.: CO136
Lot #: TC01089
Expiration Date: January 2005

2.2.3 List of Reference Standards for Protein / Amino Acid Analysis

Amino Acid Kit
CAS #: NA
Supply: Pierce
Purity: 2.5 +/- 0.1 µmol/mL for all compounds and cystine is 1.25 +/- 0.1 µmol/mL
Storage Condition: Below -4 °C
Cat. No.: NCI10180
Lot #: EH65151
Expiration Date: April 2006
Aspartic acid
Serine
Glutamic acid
Glycine
Histidine
Threonine
Arginine
Alanine
Proline
Cystine
Tyrosine

Valine
Methionine
Lysine
Isoleucine
Leucine
Phenylalanine

Protein Standard with Bovine Serum Albumin in Saline
CAS #: NA
Supply: Sigma-Aldrich
Purity: 200 mg/mL (BSA)
Storage Condition: Below -4 °C
Cat. No.: P5369
Lot #: 013k6024
Expiration Date:

3. STUDY PERSONNEL

Chee Kai Tan, Group Leader, Study Director
Radonna Spies, Group Leader
David Hererra, Senior Chemist
Lorraine Scheller, Manager

4. EXPERIMENTAL

4.1 Sample Preparation

The Explant / Implant devices were kept in the refrigerator upon receipt. The samples were removed from the refrigerator and stored in desiccators prior to splitting the samples. The whole devise was cut into four quarters. The gel from each quarter was removed from the shell by gravity and with the aid of a spatula. The individual quarter shell and gel samples were then stored in a 32 oz jar and the sample containers were labeled accordingly and stored in desiccators until analyses.

4.2 Analytical Methods

4.2.1 Moisture Content Analysis for Shell and Gel Samples

The water content in the gel and shell samples was determined using [redacted] TAP-01-0406-131. A Fisher Scientific Accumet Model 150 Titration Control with Denver Instrument Model 275KF Coulometric Karl Fisher Titrator was used for the analysis and each of the samples was analyzed in duplicate.

The one-quarter portion of the shell was dissected into 2mm x 2mm pieces. The sample was mixed well and a portion of the sample (approximately 1g) was used for the analysis. The shell sample was introduced into the Karl Fisher titrator directly. Duplicate analyses were performed for the shell sample and the average of the two results was reported.

For gel sample, a 1g portion of the gel sample was obtained from different location of the one-quarter of the gel sample for a representative sample. The sample was thinly smeared into the bottom of the 40 mL VOA vial. The moisture of the sample was extracted with 10 mL of anhydrous methanol; then 0.5 mL of the methanol extract was injected into the Karl Fisher titrator. Although anhydrous methanol was used, four methanol blanks were prepared and extracted exactly like the sample to correct for any water resulting from atmospheric humidity. Each extracted sample was corrected for the average water content in the four blanks. Each sample was prepared, extracted and analyzed in duplicate; the average of the two results was reported.

4.2.2 Amino Acids / Protein Analysis for Shell and Gel Samples

The amino acids in the gel and shell samples were determined using [redacted] TAP-01-0408-078, acid hydrolysis of protein and followed with amino acids assay with a liquid chromatograph. The shell sample was desiccated prior to extraction and it was weighed and recorded prior to and after extraction. Soxhlet extraction was performed using [redacted] SOP GLP-01-11-64 with a shell sample mass to solvent volume (M/V) ratio of 1/25 with hexane as the extraction solvent. Approximately 1.0g of the shell was extracted and at the end of the extraction, the final volume of the shell extract was adjusted to 5 mL. The hexane extract sample was then analyzed for fat by FT-IR, Part 4.2.3.

Followed [redacted] TAP-01-0408-078, the extracted shell sample (300mg) was acid hydrolyzed with 5 mL of 6N HCl for a complete protein hydrolysis. Hydrolysis occurred at 110°C for 24 hours. A 1:20 dilution of the hydrolysate was made and 1 mL of the diluted sample was filtered with 5 µL taken for derivatization. Duplicate sample analysis was performed for the shell sample and matrix spike recovery was performed on the shell sample.

For gel sample, the sample was hydrolyzed without hexane extraction. Approximately 300mg of the representative sample was obtained and directly hydrolyzed with 5 mL of 6N HCl for a complete

protein hydrolysis. Similarly, a 1:20 dilution of the hydrolysate was made and 1 mL of the diluted sample was filtered with 5 µL taken for derivatization. Sample was analyzed in duplicate and matrix spike recovery was performed for the gel sample.

Both shell and gel acid hydrolyzed samples were analyzed for amino acids according to [redacted] TAP-01-0408-078. The protein content was calculated by summing each individual amino acid concentration detected.

4.2.3 Fat Content Analysis for Shell and Gel Samples

Soxhlet extraction was performed using [redacted] SOP GLP-01-11-64 with a shell sample mass to solvent volume (M/V) ratio of 1/25 with hexane as the extraction solvent. Approximately 1.0g of the shell was extracted and at the end of the extraction, the final volume of the shell extract was adjusted to 5 mL. The hexane extract sample was then analyzed for fat by FT-IR, Part 4.2.3.

The fat content was determined according to [redacted] TAP-01-0203-035 using corn oil in hexane as the calibration standards (5 levels). The hexane was also scanned as a control blank for background correction. The standards and the extracts of fat and gel samples were scanned in the range of 1830 – 1580 cm^{-1}. The absorbance intensity at 1751 cm^{-1} was recorded (C=O stretch vibration of the carboxyl functional group of fatty acids) for fat determination. The fat content was measured with the FTIR instrument named Nicolet Magna – IR 560 Spectrometer with Spetra-Tech EZ-Fill Demountable potassium bromide window Cell Kit. For shell samples, the hexane extract samples from Part 4.2.2 were analyzed directly.

For gel sample, approximately 6g of the sample were spread in the center of a prewashed (with water and methylene chloride), predesiccated, and preweighed Teflon fabric sheeting (12" x 12", Fluortex ETFE screening fabrics, product number 9-70/22", 70 microns mesh opening, Tetco Inc.). The four edges of the sheeting was grabbed and made into a bag and tied with Teflon beadings (0.47" diameter, Cole Parmer). The sample was then extracted in a Soxhlet extractor with hexane with a sample mass to solvent volume (M/V) ratio of 1/150. At the end of the extraction, the final gel sample volume was adjusted to 15 mL in hexane and proceeded for fat analysis. The weight of the gel sample was recorded prior the extraction.

4.3 Quantitation, Calculations and Statistical Methods

4.3.1 Moisture Content Analysis for Shell and Gel Samples

For shell sample, the concentration was calculated:

Concentration, mg/Kg (ppm) = (µg detected from the titration / sample weight, g)

For gel sample, the concentration was calculated as follows:

$$\text{Moisture Conc., ppm} = \frac{(\mu g \text{ detected from titration} - \mu g \text{ in methanol}) \times 10mL/0.5mL}{\text{Sample Weight, g}}$$

Where 10mL = Extraction volume of methanol for gel sample, and
0.5mL is the amount of the extract used for the analysis

4.3.2 Amino Acids / Protein Analysis for Shell and Gel Samples

A five-point calibration standard curve was used for the initial calibration. Concentration of amino acid was quantified from the linear equation, $y = mx + b$, where

y = ppm concentration of amino acid of a sample,
m = the slope of the line,
x = intensity of the peak of individual amino acid, and
b = the y-intercept

4.3.3 Fat Content Analysis for Shell and Gel Samples

For shell sample, the % Fat was calculated:

$$\%\text{ Fat (wt / wt)} = \frac{\%\text{ Fat (wt / vol)} \times \text{Extraction Final Volume (5 mL)}}{\text{Sample weight (g)}}$$

For gel sample, the % Fat was calculated:

$$\%\ \text{Fat (wt / wt)} = \frac{\%\ \text{Fat (wt / vol)} \times \text{Extraction Final Volume (15 mL)}}{\text{Sample weight (g)}}$$

Where % Fat (wt / vol) was quantified from the linear equation, $y = mx + b$, with a set of standards prepared in hexane, where

y = % concentration of fat (wt / vol) of a sample,
m = the slope of the line,
x = the absorbance of a sample, and
b = the y-intercept

4.4 Method Detection Limit (MDL) Study

4.4.1 Moisture Content and Amino Acids

Method Detection Limit (MDL) for moisture content was performed according to 40 CFR Part 136 Appendix B. For shell sample, the MDL was determined directly by analyzing seven replicate injections of 5.0 mg/mL water standard. The mean (X), standard deviation (S) and the MDL were then calculated over the seven replicate analyses. The reporting limit (RL) was then established at three times the MDL.

$$X = \frac{\Sigma\, Xi}{N}, \quad S = \left\{\frac{\Sigma\,(Xi - X)^2}{N - 1}\right\}^{1/2}, \quad MDL = S \times t \text{ value}$$

Where Xi represent the individual values for a set of N replicate measurements and t is 3.143 for seven replicates.

For gel analysis, the Method Detection Limit (MDL) for moisture content was calculated based on 200 µL of the 5.0 mg/L water extracted with 10 mL of anhydrous methanol and 1 g of the sample weight. Similar to the sample analysis, 0.5 mL of the methanol extract was injected into the Karl Fisher titrator. The MDL results were corrected for the methanol blank.

The Limit of Detection (LOD) and Limit of Quantitation for the amino acids assay was calculated by analyzing ten replicates of hydrolyzed and derivatized standard at the lowest level of the calibration curve. The LOD and LOQ were calculated per FDA/ICH guidance for method validation. The

standard deviation of the ten analyses was calculated and the LOD determined to be the result of the standard deviation times 3.3 divided by the slope of the calibration curve. The LOQ was determined to be the result of the standard deviation times 10 divided by the slope of the curve. These values were adjusted for extraction conditions consisting of 300mg taken to a final volume of 2100 mL.

4.4.2 Fat

For fat analyses, the MDL was calculated based on the lowest response of the lowest concentration in a standard calibration curve as follows:

Instrument Detection Limit (IDL) = conc of std / pk-pk S/N x 3
Reporting Detection Limit (RDL) = conc of std / pk-pk S/N x 10
Method Detection Limit (MDL) = RDL x volume (mL) / sample wt (g)

5. PROCEDURAL MODIFICATION AND NOTICE

Moisture Content Study, TAP-01-0406-131 5.9.6.3 Gel Sample 5.9.6.3.2 and Study Protocol Number GLP-SP-002.3 Test System, use methanol (Acros Research Products, Lot Number B0507242) to extract moisture from the gel sample. Study Protocol GLP-SP-002.2 Test and Reference Substances B. Reference Substance, change water reference standard from Sigma-Aldrich to Aqualine Water Standard, 5 mg/L, Fisher Lot Number 025848.

Procedure for hydrolysis of shell and gel samples was changed from the protocol [redacted] GLP GLP 01-11-73 to [redacted] TAP 01-0408-078. Gel sample was not extracted for fat prior to hydrolysis.

6. RESULTS AND DISCUSSION

6.1 Moisture Content

The average moisture content results and spiked recoveries of the shell and gel samples are presented in Table 1. Duplicate analytical data of individual sample are attached in Appendix C. Moisture was detected in shell samples in the range of 1090 – 1580 ppm for individual results. Moisture was detected below detection limit of the gel samples. In general, the moisture content was detected in shell samples but not in the gel and moisture contents in the shell samples contained relatively equal amount of moisture.

Table 1. Average Moisture Content Detected in The Gel-Filled Explant and Control Implant Devices (Shell and Gel Samples)

SHELL AND GEL MOISTURE CONTENT					
Device Traceability	P/N 350-7450BC	P/N 354-2507	P/N 354-3507	P/N 350-7250BC	P/N 354-1007
Cat. No. /Lot No.	L/N 47073	L/N 50938	L/N 57883	L/N 57529	L/N 60228
Device Description	Smooth Round (Explant)	Siltex Round (Explant)	Siltex Round (Explant)	Smooth Round (Control)	Siltex Round (Control)
Traceability (Size/Days in Vivo)	450cc/1,290	250cc/2,330	350cc/3,249	250cc/NA	100cc/NA
Shell Sample ID	411001	411003	411005	411007	411009
Shell Average Moisture Content, ppm (mg/Kg)	1,360	1,210	1,565	1,350	1,210
Shell Matrix Spike Recovery, ppm (mg/Kg) (% Recovery)					2,330 (95.8% Recovery)
Gel Sample ID	411002	411004	411006	411008	411010
Gel Moisture Content, ppm (mg/Kg)	<1038	<1080	<1027	<998	<1015
Gel Matrix Spike Recovery, ppm (mg/Kg) (% Recovery)					10,500 (106% Recovery)

The whole device's moisture content was calculated and established in Table 2.

Table 2. Whole Device Moisture Content of Smooth Round Moderate Profile Gel-Filled Mammary Implants (Explants and Controls)

WHOLE DEVICE					
Device Traceability	P/N 350-7450BC	P/N 354-2507	P/N 354-3507	P/N 350-7250BC	P/N 354-1007
Cat. No. /Lot No.	L/N 47073	L/N 50938	L/N 57883	L/N 57529	L/N 60228
Device Description	Smooth Round (Explant)	Siltex Round (Explant)	Siltex Round (Explant)	Smooth Round (Control)	Siltex Round (Control)
Traceability (Size/Days in Vivo)	450cc/1,290	250cc/2,330	350cc/3,249	250cc/NA	100cc/NA
Shell Sample ID	411001	411003	411005	411007	411009
Gel Sample ID	411002	411004	411006	411008	411010
Moisture Content, ppm	192.4	219.6	279.3	236.6	252.6

Note: The moisture content of the whole device was calculated using the equation:
Whole Device, ppm = (Shell Conc. x Shell Amount + Gel Conc. x Gel Amount)/(Shell Amount + Gel Amount)

6.2 Protein/Amino Acids Content

The average protein content results and spiked recoveries of the shell and gel samples are presented

in Table 3. Duplicate analytical data of individual sample are attached in Appendix C. Protein was not detected in shell and gel samples for the explant and unimplanted control samples.

Table 3. Average Protein/Amino Acids Content Detected in The Gel-Filled Explant and Control Implant Devices (Shell and Gel Samples)

SHELL AND GEL PROTEIN CONTENT					
Device Traceability	P/N 350-7450BC	P/N 354-2507	P/N 354-3507	P/N 350-7250BC	P/N 354-1007
Cat. No. /Lot No.	L/N 47073	L/N 50938	L/N 57883	L/N 57529	L/N 60228
Device Description	Smooth Round (Explant)	Siltex Round (Explant)	Siltex Round (Explant)	Smooth Round (Control)	Siltex Round (Control)
Traceability (Size/Days in Vivo)	450cc/1,290	250cc/2,330	350cc/3,249	250cc/NA	100cc/NA
Shell Sample ID	411101	411103	411105	411107	411109
Shell Average Protein Content, ppm (mg/Kg)	<500	<500	<500	<500	<500
Shell Matrix Spike Recovery, ppm (mg/Kg) (% Recovery)					68,411 (79% Recovery)
Gel Sample ID	411102	411104	411106	411108	411110
Gel Protein Content, ppm (mg/Kg)	<500	<500	<500	<500	<500
Gel Matrix Spike Recovery, ppm (mg/Kg) (% Recovery)					67,494 (78% Recovery)

The whole device's protein/amino acids content was calculated and established in Table 4.

Table 4. Whole Device Protein/Amino Acids Content of Smooth Round Moderate Profile Gel-Filled Mammary Implants (Explants and Controls)

WHOLE DEVICE					
Device Traceability	P/N 350-7450BC	P/N 354-2507	P/N 354-3507	P/N 350-7250BC	P/N 354-1007
Cat. No. /Lot No.	L/N 47073	L/N 50938	L/N 57883	L/N 57529	L/N 60228
Device Description	Smooth Round (Explant)	Siltex Round (Explant)	Siltex Round (Explant)	Smooth Round (Control)	Siltex Round (Control)
Traceability (Size/Days in Vivo)	450cc/1,290	250cc/2,330	350cc/3,249	250cc/NA	100cc/NA
Shell Sample ID	411001	411003	411005	411007	411009
Gel Sample ID	411002	411004	411006	411008	411010
Protein Content, ppm	<500	<500	<500	<500	<500

Note: The protein content of the whole device was calculated using the equation:
Whole Device, ppm = (Shell Conc. x Shell Amount + Gel Conc. x Gel Amount)/(Shell Amount + Gel Amount)

6.3 Fat Content

The average fat content results and spiked recoveries of the shell and gel samples of explant and unimplanted control devices are presented in Table 5. Individual sample fat results of duplicate analytical data are attached in Appendix C. Fat was detected in explanted shell samples in the range of 1989 – 2419 ppm (except explant sample 47073). For gel samples, fat was detected below detection limit for both explant and control unimplanted matrices. In general, the fat content was detected in the explanted shells but not in the gel samples. The fat contents among the shell samples contained relatively equal amount of fat for the explant and control samples.

Table 5. Average Fat Content Detected in The Gel-Filled Explant and Control Implant Devices (Shell and Gel Samples)

SHELL AND GEL FAT CONTENT					
Device Traceability	P/N 350-7450BC	P/N 354-2507	P/N 354-3507	P/N 350-7250BC	P/N 354-1007
Cat. No. /Lot No.	L/N 47073	L/N 50938	L/N 57883	L/N 57529	L/N 60228
Device Description	Smooth Round (Explant)	Siltex Round (Explant)	Siltex Round (Explant)	Smooth Round (Control)	Siltex Round (Control)
Traceability (Size/Days. in Vivo)	450cc/1,290	250cc/2,330	350cc/3,249	250cc/NA	100cc/NA
Shell Sample ID	411001	411003	411005	411007	411009
Shell Average Fat Content, ppm (mg/Kg)	<250	2,204	2,323	<250	<250
Shell Matrix Spike Recovery, ppm (mg/Kg) (% Recovery)					25,613 (116.3% Recovery) Sample #6 Siltex Round (Unimplanted, unautoclaved)
Gel Sample ID	411002	411004	411006	411008	411010
Gel Fat Content, ppm (mg/Kg)	<250	<250	<250	<250	<250
Gel Matrix Spike Recovery, ppm (mg/Kg) (% Recovery)				16,244 (82.7% Recovery)	

The whole device's moisture content was calculated and established in Table 6.

Table 6. Whole Device Fat Content of Smooth Round Moderate Profile Gel-Filled Mammary Implants (Explants and Controls)

FAT CONTENT OF WHOLE DEVICE					
Device Traceability	P/N 350-7450BC	P/N 354-2507	P/N 354-3507	P/N 350-7250BC	P/N 354-1007
Cat. No. /Lot No.	L/N 47073	L/N 50938	L/N 57883	L/N 57529	L/N 60228

FAT CONTENT OF WHOLE DEVICE					
Device Description	Smooth Round (Explant)	Siltex Round (Explant)	Siltex Round (Explant)	Smooth Round (Control)	Siltex Round (Control)
Traceability (Size/Days in Vivo)	450cc/1,290	250cc/2,330	350cc/3,249	250cc/NA	100cc/NA
Shell Sample ID	411001	411003	411005	411007	411009
Gel Sample ID	411002	411004	411006	411008	411010
Fat Content, ppm	<250	600.4	546.5	<250	<250

Note: The fat content of the whole device was calculated using the equation:
Whole Device, ppm = (Shell Conc. x Shell Amount + Gel Conc. x Gel Amount)/(Shell Amount + Gel Amount)

7. QUALITY ASSURANCE/GOOD LABORATORY PRACTICES

[redacted] maintains a Quality Assurance Unit (QAU) in compliance with EPA's current FIFRA Good Laboratory Practices Standard (40 CFR 160). This study will be conducted according to generally accepted Good Laboratory Practices (GLP) (Federal Register, Vol 54, pp 34052-34074 (August 17, 1989). The QAU will conduct periodic inspections of this study, as well as the [redacted] facility, to assure conformance to the study protocol, standard operating procedures and GLP. The inspection results will be reported to [redacted] management, [redacted] Quality Assurance management and the [redacted] study director. Quality assurance unit activities shall be audited by [redacted] QA. The final report will be reviewed by the QAU, and a signed statement will be included which specifies the dated inspections/audits were made and reported to [redacted] management, [redacted] Quality Assurance management and the [redacted] study director.

8. RECORDS TO BE MAINTAINED

Copies of the protocol, appendices, amendments, and the analytical method shall be available to the analysts, technicians, and chemists involved in the study at [redacted] are required of TAP-01--0407-48, *Study Director Responsibilities for GLP Studies*. The analysts at [redacted] shall maintain laboratory notebooks or equivalent documents in which they will record all procedures, weighings, observations, etc., relevant to the experimental work. Chromatograms, computer printouts, etc., will be clearly labeled and notebooks will remain in the analyst's possession throughout the study. Records shall be archived as written in [redacted] SOP GLP-01-0407-052, *Record Archival for GLP Studies*.

At the completion of the analytical portion of the study, a report shall be prepared as specified in [redacted] SOP GLP-01-04077-051, Generation of Final Report for GLP Studies, and delivered to the sponsor for final approval. After completion of the final report for the study, all methodology, raw data sheets, and original chromatograms will be inspected by the QAU at [redacted] At the sponsor's

discretion, all original records will be sent to the sponsor for archiving in accordance with 21 CFR 58 Good Laboratory Practices Standards.

9. SAMPLE RETENTION

With sponsor approval, any samples remaining at the conclusion of the study can be disposed of by [redacted] personnel or returned to Mentor Corporation.

10. DISPOSITION OF RAW DATA AND SAMPLES

All raw data, including chromatograms, spreadsheets and notebooks will be indexed by the study director and forwarded to Mentor Corporation for archiving. Samples and test substances will be returned to Mentor Corporation at the conclusion of the study.

11. REFERENCE

21 CFR 58 Good Laboratory Practices Standards.
Mentor Protocol CP 411, Explant Testing: Determination of Moisture, Protein, and Fat.
[redacted] Study Protocol GLP-SP-002, Explant Testing: Determination of Moisture, Protein, and Fat.
[redacted] TAP-01-0203-035, Quantitative Determination of Fat in Explant Materials by FTIR.
[redacted] TAP-01-0206-131, Determination of Moisture by Karl Fischer Method.
[redacted] TAP-01-0408-078, HPLC Determination of Amino Acids Using The Waters ACCQ•TAG Method.

CONFIDENTIAL - TRADE SECRET

REPORT CP411ADDENDUM

EXPLANT TESTING: PLATINUM ANALYSES

Mentor Corporation
Science & Technology
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August 10, 2004

FINAL REPORT

NON-GLP PROTOCOL CP 411 ADDENDUM EXPLANT TESTING: PLATINUM ANALYSES

AUTHOR

Chee Kai Tan, Ph.D.

STUDY INITIATION DATE
May 01, 2004

STUDY COMPLETION DATE
July 30, 2004

TEST FACILITY

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STATEMENT OF CONFIDENTIALITY CLAIMS

Information is claimed confidential on the basis of its business, products, laboratory analysis and evaluation of mammary implants. The information is considered proprietary, confidential, and valuable to Mentor Corporation.

08/04/04

Grace Chiang (DATE)
Mentor Corporation

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1. INTRODUCTION

The objective of this study was to determine and compare the platinum present in the explant intact Mentor Gel-Filled Mammary Implants and the unimplanted devices. The gel samples were digested with concentrated nitric, hydrochloric and sulfuric acids. The shell samples were digested using microwave digestion with a digestion solution of de-ionized water, aqua regia and hydrofluoric acid. A Perkin Elmer Elan 5000a ICP-MS was used for the analysis. Tuning, mass calibration and mass resolution checks were performed prior to analysis to validate the instrument. Tests conducted followed Mentor non-GLP Protocol CP 411 Addendum.

2. TEST AND REFERENCE SUBSTANCES

2.1 Test Substances – Explants and autoclaved unimplanted controls of gel-filled mammary implants

Table 1. Sample List – Sample Description and Traceability

Sample No.	Description	Size	Catalog No.	File No.	Date of Implantation	Days in Vivo	Lot No.
1	Smooth Round Moderate Profile Gel-Filled Mammary Implant (Expant)	450cc	350-7450BC	971875	11/11/1993	1,290	47073
2	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Explant)	250cc	354-2507	200101-0558	Mid 1994	2,330	50938
3	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Explant)	350cc	354-3507	200302-0663	Early 1994	3,249	57883
4	Smooth Round Moderate Profile Gel-Filled Mammary (Unimplanted Control)	250cc	350-7250BC	NA	NA	NA	57529

Sample No.	Description	Size	Catalog No.	File No.	Date of Implantation	Days in Vivo	Lot No.
5	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Unimplanted Control)	100cc	354-1007	NA	NA	NA	60228
6	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Unimplanted, unautoclaved)	100cc	354-1007	NA	NA	NA	60228
7	Siltex Round Moderate Profile Gel-Filled Mammary Implant (Unimplanted, unautoclaved), for exploratory work and method applicability	100cc	354-1007	NA	NA	NA	60228

2.2 Reference Substances

2.2.1. List of Reference Standards

Tuning, Mass Calibration and Mass Resolution Check Standards
Supply: Perkin Elmer
Cat. No.: N8122014
Lot #: 2-192BD (Inorg #4594)
Expiration Date: 09/30/05

Multi-Element Solution 3
Platinum Standard in 10% HCl/1% HNO3
Supply: SPEX
Cat. No.: CLMS-3
Lot #: 7-161 Vy (Inorg #4366)
Expiration Date: 12/30/04

Precious Metals Complete Standards, 100 ppm Pt in 3.3% HCl
Supply: Inorganic Ventures
Cat. No.: CCS-2
Lot #: W-MEB156017 (Inorg #4621)
Expiration Date: 07/01/05

3. STUDY PERSONNEL

Chee Kai Tan, Group Leader, Study Director
Jackie Ranger, Group Leader

4. EXPERIMENTAL

4.1 Instrument Validation

The samples were analyzed with a Perkin Elmer Elan 5000a ICP-MS interfaced with a AS91 autosampler. At the beginning of the analysis sequence prior to sample analysis; mass tuning calibration and resolution checks were performed using the tuning solution (10 µg/L of Mg, Rh, and Pb) to validate the instrument. For these checks, a solution containing low, mid and high masses was used. Magnesium (mass 24), rhodium (mass 103) and lead (mass 208) were monitored. The tuning was used to verify that the instrument has reached thermal stability. The solution was analyzed ten times and the RSD of the signals was less than 5%. For the mass calibration check, the determined "current mass" did not differ by more than 0.1 amu from the true atomic mass unit (amu). For the mass resolution check, the determined "peak width" or resolution was less than 0.9 amu at full width at 10% peak height.

The instrument condition for mass calibration and resolution checks and sample analysis was set according to the following conditions:

RF Power: 1000W
Plasma Gas: 15 L/min.
Auxiliary Gas Flow: 0.8 L/min.

4.2 Instrument Analysis – ICP-MS Instrument Parameters for Analyzing Shell and Gel Samples

The calibration verification solution and the calibration blank were analyzed at a frequency of at least once every 10 analytical samples. The results of the initial calibration verification (ICV) and the continuing instrument check standard (CCV) were within +/-10% of the expected value.

4.3 Sample Preparation

4.3.1 Sample Preparation of Explanted and Unimplanted Control Shell Samples (Lot Numbers 47073, 50938, 57883, 57529, & 60228)

Shell sample was cut into four sections and desiccated until constant weight was attained (minimum 24 hours). Approximately 100 milligram of each shell sample were readied for analysis using microwave digestion. For digestion, 15mL of de-ionized water, 10mL of aquq regia and 2mL of hydrofluoric acid were used. For the microwave digestion, the samples were heated to a final temperature of 180°C in twenty minutes and held at that temperature for an additional twenty-five minutes. Explant sample 411208B and unimplanted control sample 411209A were analyzed as quality control samples. The quality control analyses included duplicates, matrix spikes and matrix spike duplicates. A laboratory preparation blank was digested, analyzed and reported along with the samples. In addition, two laboratory control samples or blank spikes were also digested, analyzed and reported with the samples.

4.3.2 Sample Preparation of Explanted and Unimplanted Control Gel Filler Samples (Lot Numbers 47073, 50938, 57883, 57529, & 60228)

Approximately 250 milligrams of each gel sample were digested in test tubes with concentrated nitric, hydrochloric and sulfuric acids. The acid volumes used were 0.5mL nitric, 0.5mL hydrochloric and 3mL sulfuric. The digestion was performed at 95°C-200°C for approximately 8 hours. Explant gel sample 411203B and unimplanted control sample 411204A were digested and analyzed as quality control samples. Quality control analyses included duplicates, matrix spikes and matrix spike duplicates. A preparation blank was digested, analyzed and reported along with the samples. In addition, two laboratory control samples or blank spikes were also digested, analyzed and reported with the samples.

5. CALCULATIONS

The concentrations determined in the shell and gel digest are calculated below:

Concentration (mg/Kg) = C x V/W

Where C = Digest Concentration (mg/L)
V = Final volume in liters after sample preparation
W = Weigh in Kg of the shell or gel sample

6. RESULTS AND DISCUSSIONS

The average platinum analytical results and spiked recoveries of the shell and gel samples are presented in Table 1. Duplicate analytical data of individual sample are attached in Appendix C. Platinum was detected in shell samples in the range of 6.08 – 11.6 ppm for individual results and there was not much different between the explant and unimplanted control samples. Platinum was detected in the individual gel samples, 0.174 - 0.283 ppm. In general, the platinum content was detected in shell samples and had higher concentration than the gel samples. The platinum contents among the shell samples contained relatively equal amount of platinum as well as the gel samples.

Table 1. Average Platinum Content Detected in The Gel-Filled Explant and Control Implant Devices (Shell and Gel Samples)

SHELL AND GEL PLATINUM CONTENT					
Device Traceability	P/N 350-7450BC	P/N 354-2507	P/N 354-3507	P/N 350-7250BC	P/N 354-1007
Cat. No. /Lot No.	L/N 47073	L/N 50938	L/N 57883	L/N 57529	L/N 60228
Device Description	Smooth Round (Explant)	Siltex Round (Explant)	Siltex Round (Explant)	Smooth Round (Control)	Siltex Round (Control)
Traceability (Size/Days in Vivo)	450cc/1,290	250cc/2,330	350cc/3,249	250cc/NA	100cc/NA
Shell Sample ID	411206	411207	411208	411209	411210
Shell Average Platinum Content, ppm (mg/Kg)	10.130	6.285	6.165	7.795	10.135
Shell Matrix Spike Recovery, ppm (mg/Kg) (% Recovery)			17.5 (96.0% Recovery)		
Gel Sample ID	411201	411202	411203	411204	411205
Gel Platinum Content, ppm (mg/Kg)	0.245	0.283	0.252	0.208	0.176
Gel Matrix Spike Recovery, ppm (mg/Kg) (% Recovery)			2.34 (87.2% Recovery)		

The whole device's platinum content was calculated and established in Table 2:

Table 2. Whole Device Platinum Content of Smooth Round Moderate Profile Gel-Filled Mammary Implants (Explants and Controls)

WHOLE DEVICE					
Device Traceability	P/N 350-7450BC	P/N 354-2507	P/N 354-3507	P/N 350-7250BC	P/N 354-1007
Cat. No. /Lot No.	L/N 47073	L/N 50938	L/N 57883	L/N 57529	L/N 60228
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Traceability (Size/Days in Vivo)	450cc/1,290	250cc/2,330	350cc/3,249	250cc/NA	100cc/NA
Shell Sample ID	411206	411207	411208	411209	411210
Gel Sample ID	411201	411202	411203	411204	411205
Platinum Content, ppm	2.781	2.080	2.037	2.400	3.316

Note: The platinum content of the whole device was calculated using the equation:
Whole Device, ppm = (Shell Conc. x Shell Amount + Gel Conc. x Gel Amount)/(Shell Amount + Gel Amount)

7. SAMPLE RETENTION

With sponsor approval, any samples remaining at the conclusion of the study can be disposed of by [redacted] personnel or returned to Mentor Corporation.

8. DISPOSITION OF RAW DATA AND SAMPLES

All raw data, including chromatograms, spreadsheets and notebooks will be indexed by the study director and forwarded to Mentor Corporation for archiving. Samples and test substances will be returned to Mentor Corporation at the conclusion of the study.

9. REFERENCE

[redacted] TAP 01-0406-046 SW-846 Method 6020 Inductively Coupled Plasma Mass Spectrometry Analysis

CONFIDENTIAL - TRADE SECRET

REPORT CP411ADDENDUM

EXPLANT TESTING: PLATINUM ANALYSES

Mentor Corporation
Science & Technology
201 Mentor Dr.
Santa Barbara, CA 93111

August 10, 2004

FINAL REPORT

NON-GLP PROTOCOL CP 411 ADDENDUM EXPLANT TESTING: PLATINUM ANALYSES

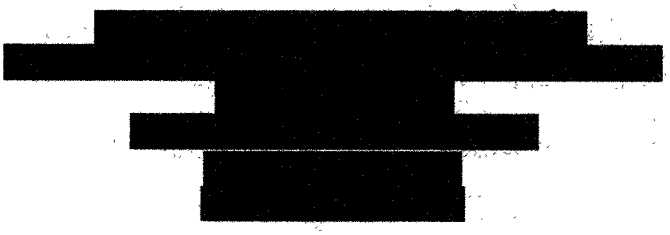
AUTHOR

Chee Kai Tan, Ph.D.

STUDY INITIATION DATE
May 01, 2004

STUDY COMPLETION DATE
July 30, 2004

TEST FACILITY



PROJECT NUMBER

01.10258.04.00X

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9. REFERENCE

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